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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BAUM, STUART F

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 04/23/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,992	SALTVEIT ET AL.	
	Examiner	Art Unit	
	Stuart F. Baum	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-5,9-13 and 15-20* is/are pending in the application.

4a) Of the above claim(s) *18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9-13 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *with application* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. Claims 1-5, 9-13, and 15-20 are pending.

2. Applicant's election with traverse of Group I, claims 1-5, 9-13, and 15-17, including SEQ ID NO:3 encoding SEQ ID NO:1 in Paper No. 17 is acknowledged. The traversal is on the ground(s) that according to the MPEP, the Examiner must examine claims even though they are directed to independent and distinct inventions and Applicant contends that all claims can be searched without undue burden. This is not found persuasive because while the search of the prior art for one group may overlap with that of another, they are not co-extensive of each other and thus would be a burden on the Office.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 18-20 are withdrawn from consideration for being drawn to non-elected inventions.

Claims 6-8, 14, and 21-23 have been canceled.

4. Claims 1-5, 9-13 and 15-17 are examined in the present office action.

Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See for example page 10, 4th paragraph. See MPEP § 608.01.

Information Disclosure Statement

6. The U.S. patents, WO document, and publications numbered D8-D40 listed on form 1449 have not been considered as they were not provided by the Applicant. As stated in the MPEP § 1.98 (a) Any information disclosure statement filed under § 1.97 shall include: (1) A list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) A legible copy of:

(i) Each U.S. patent application publication and U.S. and foreign patent;

(ii) Each publication or that portion which caused it to be listed;

Claim Objections

7. Claim 16 is objected to for reading on a non-elected sequence. Correction is required.

8. In claim 16, Applicant has specified SEQ ID NO:2, which is a protein sequence even though the claim is drawn to a DNA sequence. For reasons of compact prosecution, the Examiner is reviewing the claim as being drawn to SEQ ID NO:3 instead of SEQ ID NO:2. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-5, 9-13 and 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, it is unclear whether the fragment thereof must also encode SEQ ID NO:1. For examination purpose, the Office interprets that the fragment thereof must encode SEQ ID NO:1. If such is not Applicant's intention, claim 1 should be amended accordingly.

Claim 2 does not further limit claim 1 as claim 2 only requires 18 base pairs of the nucleotide sequence encoding SEQ ID NO:1 of claim 1.

In claim 2, it is unclear whether the 18 base pairs is from SEQ ID NO:3 or from the nucleotide sequence encoding SEQ ID NO:1.

Claims 2 and 3 are indefinite as it is not clear how a fragment consisting of 18-500 nucleotides can encode a polypeptide consisting of 711 amino acids. Also, does the fragment comprising 18 to 500 base pairs refer to SEQ ID NO:3 or to a nucleic acid sequence encoding SEQ ID NO:1?

Claim 3 does not further limit claim 2 because the "18 base pairs up to full length" of claim 2 is longer than "between 18 to 500 base pairs" of claim 3.

In claim 4, Applicant has a negative limitation drawn to a nucleotide sequence as shown in Figure 2, but Figure 2 only shows amino acid sequences. In addition, according to 37 CFR 1.821(d), claim 4 requires the use of an assigned sequence identifier (e.g. SEQ I.D. NO: X).

In claim 4, it is unclear what "other" refers to.

In claim 4, the metes and bounds of "stringent hybridization conditions" are not defined in the claim. Conditions defining "stringent hybridization" differ from artisan to artisan, and as such, the conditions which Applicant defines as "stringent" should be explicitly stated in the claim.

In claim 5, it is unclear how a nucleic acid fragment contains an enzyme or a protein.

In claim 5, the metes and bounds of "a particle" have not been defined. What constitutes "a particle"? What are the size dimensions of "a particle"?

In claim 9, the metes and bounds of "transcriptional initiation sequence" have not been defined. Does the "transcriptional initiation sequence" comprise elements that specify temporal, constitutive or inducible expression? Does Applicant mean a promoter? All subsequent recitations of "transcriptional initiation sequence" are also rejected.

In claim 10, since neither the construct nor the vector is defined, it is unclear how they differ.

Claim 12 is an improper dependent claim because claim 11 is not drawn to a transcriptional initiation sequence.

In claim 12, the recitation "wound induced expression" is unclear. Does Applicant mean that the transcriptional initiation sequence causes wound induction, or that SEQ ID NO:3 causes wound induction, or that the transcriptional initiation sequence causes SEQ ID NO:3 to be expressed when a wound is induced? Clarification is required.

In claim 15, the metes and bounds of "enzymatically active fragment" have not been defined. Applicants have not specified the enzyme function associated with the polypeptide of SEQ ID NO:3.

In claim 15, open reading frames are not expressed. Nucleic acid sequences encoding open reading frames are expressed.

In claim 15, the recitation "altered" is unclear. Applicant needs to explicitly state how the phenylalanine ammonia-lyase has been changed.

In claims 16 and 17, the recitation "open reading frame" should be replaced with --the nucleotide sequence--.

In claim 17, the recitation "increase" lacks a comparative basis. Also, it is unclear where the "increase" takes place. Is Applicant referring to a particular cell, tissue, or organ?

The claims are replete with idiomatic errors which make claim interpretation difficult. A complete and careful revision of all claims is suggested.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 4-5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a nucleic acid fragment that hybridizes to SEQ ID NO:3 or a method of producing a transgenic cell having altered phenylalanine ammonia lyase levels comprising a nucleic acid sequence encoding an enzymatically active fragment of SEQ ID NO:1. The specification only discloses the nucleic acid sequence of SEQ ID NO:3 encoding SEQ ID NO:1 and does not disclose any specific structural, physical and/or chemical properties for the claimed sequence. Applicants do not present a description of domains that are specific to SEQ ID NO:1 nor domains that are important for its proper function. Given the lack of description,

one skilled in the art would not be able to identify sequences with less than 100% sequence identity that still maintained the proper activity. The claims recite sequences that hybridize to SEQ ID NO:3, but Applicant has not disclosed a representative number of species as encompassed by the claims. The claims encompass mutants and allelic variants and thus imply that structural variants exist in nature, yet no structural variant has been disclosed. The implication is that there is a gene and a protein other than that disclosed which exists in nature, but the structure thereof is not known. Thus, there is insufficient relevant identifying characteristics to allow one skilled in the art to predictably determine such mutants and allelic variants from other plants and organisms, absent further guidance. Therefore, the written description requirement is not satisfied. Therefore, one skilled in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention. (see Written Description Requirement published in Federal Register/Vol.66, No. 4/ Friday, January 5, 2001/Notices; p. 1099-1111).

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-5, 9-13 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to an isolated nucleic acid sequence encoding SEQ ID NO:1, a nucleic acid sequence of SEQ ID NO:3 encoding SEQ ID NO:1, a fragment of at least 18 base pairs encoding SEQ ID NO:1, a fragment that hybridizes to SEQ ID NO:3, a fragment that hybridizes SEQ ID NO:3 and can be used as a probe, a method of producing a transgenic cell having any level of phenylalanine ammonia-lyase (PAL), wherein the cell has antifungal, antibacterial and insecticidal activity.

The claimed invention is not supported by an enabling disclosure taking into account the *In re Wands* factors (858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Applicants isolated their invention from a *Lactuca sativa* cDNA library, by performing PCR reactions using degenerate primers that were designed for PCR based on peptide sequences which were similar among sunflower, *Arabadopsis,* parsley, carrot tobacco, wheat and rice PAL sequences (page 19, Example 1). Two sequences were isolated and designated LsPAL1 and LsPAL2 and are induced in wounded lettuce tissue. The clones were expressed in bacteria and were found to encode enzymatically active polypeptides.

Applicants have not reduced to practice their invention. Applicants have only shown that PAL is expressed in wounded lettuce tissue and that PAL is an enzyme upstream of many

products that are derived from phenylalanine (Figure 1). Applicants have not taught how one skilled in the art would use plants transformed with SEQ ID NO:3 nor have Applicants taught how one skilled in the art would use SEQ ID NO:3 to generate a specific agronomically important plant. The claims are drawn to a method for increasing the levels of PAL wherein the increased acitivity results in an increase in antifungal, antibacterial or insecticidal acitivity, but Applicants have not presented any guidance, data or examples exemplifying their claims. Applicants teach the presence of PAL activity in lettuce plants, but Applicants have not specifically addressed how a cloned lettuce PAL can be used in a plant or any cell to achieve a specific phenotype or biological process.

In claim 2, Applicants claim an 18 base pair sequence encoding the amino acid sequence of SEQ ID NO:1. This claim encompasses degenerate DNA encoding SEQ ID NO:1, but Applicant has not taught degenerate sequences encoding SEQ ID NO:1. It is not clear what one skilled in the art would do with an 18 base pair sequence. Applicant has not enabled said sequence as a primer or probe, nor has Applicant enabled the sequence to be used in antisense technologies nor has Applicant enabled said sequence to be used in protein expression.

In claim 17, Applicants claim a nucleotide sequence encoding an open reading frame to be used as an antifungal, antibacterial or insecticidal molecule, but to date, there is not a single molecule known that gives resistance to all fungi, or all bacteria or to all insects. Applicants also have not disclosed the required level of expression that is necessary to achieve the desired results as it is known in the art that for many processes, a threshold of expression is required before the process can be initiated.

Applicants claim a fragment that hybridizes to SEQ ID NO:3, or a fragment that hybridizes to SEQ ID NO:3 wherein the fragment is used as a probe, but hybridization reactions do not always produce predictable results. Isolating DNA fragments using stringent hybridization conditions, does not always select for DNA fragments whose contiguous nucleotide sequence is the same or nearly the same as the probe. Fourgoux-Nicol et al (1999, Plant Molecular Biology 40 :857-872) teach the isolation of a 674bp fragment using a 497bp probe incorporating stringent hybridization conditions comprising three consecutive 30 minute rinses in 2X, 1X and 0.1X SSC with 0.1% SDS at 65^0C (page 859, left column, 2^{nd} paragraph). Fourgoux-Nicol et al also teach that the probe and isolated DNA fragment exhibited a number of sequence differences comprising a 99bp insertion within the probe and a single nucleotide gap, while the DNA fragment contained 2 single nucleotide gaps and together the fragments contained 27 nucleotide mismatches. Taking into account the insertions, gaps and mismatches, the longest stretch of contiguous nucleotides to which the probe could hybridize consisted of 93bp of DNA (page 862, Figure 2). In the present example, the isolated fragment exhibits less than 50% sequence identity with the probe.

Transforming plant cells with a PAL cDNA causes unpredictable results. Matsuda et al (1996, Plant and Cell Physiology 37(2):215-222) teach transforming tobacco with a potato PAL cDNA reduced the fertility of some of the tobacco plants. The ectopic PAL activity caused a reduction in pollen fertility (abstract). "The distorted pollen grains that did not germinate lacked starch and flavonols".

Applicants have claimed an isolated nucleic acid that encodes SEQ ID NO:1 and then in subsequent claims, Applicants claim a fragment of at least 18 base pairs up to the full length of

the open reading frame or a fragment that is between 18 and 500 base pairs, all of which still encodes SEQ ID NO:1 which is 711 amino acids. It is unclear how a fragment of 18 base pairs can encode a 711 amino acid polypeptide or even how a 500 base pair sequence can encode said polypeptide.

Given the state-of-the-art that teaches transforming plants with a PAL cDNA produces unexpected results for the reasons as stated above; given the state-of-the-art that teaches isolating or detecting fragments by hybridization techniques does not always generate sequences with the same nucleic acid sequence as the probe for the reasons stated above; given the lack of guidance and examples for how one would use a plant transformed with a nucleic acid sequence encoding SEQ ID NO:1; given the lack of examples and guidance for generating a cell with altered PAL levels or altered PAL levels and increased antifungal, antibacterial and insecticidal acitivities for the reasons stated above, it would require undue experimentation by one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Appert et al (1994, Eur. J. Biochem. 225:491-499).

The claims are drawn to a nucleic acid fragment that hybridizes to SEQ ID NO:3 under stringent conditions or a nucleic acid fragment that hybridizes to SEQ ID NO:3 wherein the fragment contains a label for detection. Claim 4 reads on a 2 base pair nucleic acid sequence.

Appert et al teach PAL-3 that exhibits 52% sequence identity to SEQ ID NO:3 and would hybridize to SEQ ID NO:3. Appert et al also teach an incomplete PAL-3 cDNA that was used as a probe, and because it was used as a probe, it would inherently contain one of the labels recited in the claim (i.e., a radioisotope, an enzyme, a particle and a protein) and it would hybridize to SEQ ID NO:3, and as such, anticipates the claimed invention.

13. Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Okada et al (September, 1999, US Patent Number 5,952,489)

Because of the 112 2nd paragraph indefiniteness of claim 12, the Office is interpreting claim 12 to be directed to any promoter that induces expression of SEQ ID NO:3.

Okada et al teach a promoter sequence that would also be considered a transcriptional initiation sequence and that could be used to induce expression of SEQ ID NO:3.

14. SEQ ID NO:3 encoding SEQ ID NO:1 is deemed free of the prior art, given the failure of the prior art to teach or reasonably suggest an isolated polynucleotide of SEQ ID NO:3 encoding SEQ ID NO:1.

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart Baum whose telephone number is (703) 305-6997. The examiner can normally be reached on Monday-Friday 8:30AM – 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 or (703) 305-3014 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist, who may be contacted at 308-0196.

Stuart F. Baum Ph.D.

April 17, 2003

4/18/03

EXAMINER